synthesis of I as described[8] was allowed to react with Boc-Lys(Z)-OH (1.95 g), pyridine (0.4 ml), and DCC (1.1 g) in CH_2Cl_2 for 2 h to give 6.0 g of Boc-Lys(Z)-OCH_2-C_6-H_4-resin (3.24 mmol). After benzoylation[15] at 0 °C for 15 min with 0.83 ml of pyridine and 0.98 ml of benzoyl chloride in 60 ml of CH_2Cl_2 the resin was deprotected (50% TFA in CH_2Cl_2, 30 min), neutralized (10% Et_3N in CH_2Cl_2, 10 min), and coupled (120 min) with Boc-His(Tos)-OH·DCHA (5.4 g, 8.1 mmol)[22] in the presence of DCC (1.69 g). The synthetic cycle was repeated again with 8.1 mmol each of Z-Gly-OH (1.7 g) and DCC (1.69 g) to give 6.9 g of Z-Gly-His(Tos)-Lys(Z)-OCH_2-C_6H_4-resin. Ammonolysis in 450 ml of NH_3-saturated MeOH for 70 h provided a partially crystalline precipitate. It was concentrated to a smaller volume, diluted with an equal volume of DMF, filtered to remove the resin particles, and evaporated to a solid mass. Crystallization from DMF with MeOH gave 1.31 g (64%) of the desired compound: mp 210–212 °C; $[\alpha]^{25}D$ −8.51° (*c* 1, DMF); the NMR spectrum agreed with the structure.

Anal. Calcd for $C_{30}H_{37}N_7O_7$ (607.6): C, 59.30; H, 6.14; N, 16.14. Found: C, 59.24; H, 6.09; N, 16.16.

Acknowledgments. The authors thank Dr. R. B. Merrifield and Dr. J. Meienhofer for discussions, and Dr. F. Scheidl, Dr. T. Williams, Dr. V. Toome, Mr. Traiman, and their colleagues for physicochemical measurements.

Registry No.—I, 54276-64-1; III, 59790-71-5; IV, 54647-58-4; V, 54276-67-4; VI, 57471-75-7; Boc-Thr(Bzl)-OH, 15260-10-3; Boc-Tyr(Bzl)-OH, 2130-96-3; Boc-Phe-OH, 13734-34-4; Boc-Gly-OH, 4530-20-5; Z-Gly-OH, 1138-80-3; Bpoc-Tyr(Bzl)-OH, 25692-91-5; Bpoc-Phe-OH, 40099-50-1; H-Thr-OCH_3, 59790-72-6; H-Thr-OH, 72-19-5; Boc-Tyr(Bzl)-Thr-OCH_3, 3373-59-9; H-Tyr(Bzl)-Thr-OCH_3·HCl, 57471-73-5; Boc-Phe-Phe-OH, 13122-90-2; H-Phe-OH, 63-91-2; Boc-Phe-OSu, 3674-06-4; Z-Gly-Phe-Ph-OH, 57471-71-3; Z-Gly-OSu, 2899-60-7; Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-Thr-OCH_3, 57471-74-6; Z-Gly-His-Lys(Z)-NH_2, 59790-73-7; Boc-Lys(Z)-OH, 2389-45-9; copolystyrene–divinylbenzene, 9003-70-7.

References and Notes

(1) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(2) R. B. Merrifield, J. M. Stewart, and N. Jernberg, *Anal. Chem.*, **38**, 1905 (1966).
(3) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969.
(4) R. B. Merrifield in "Chemistry of Polypeptide", P. G. Katsoyannis, Ed., Plenum Press, New York, N.Y., 1973, pp 335–361.
(5) J. Meienhofer in "Hormonal Proteins and Peptides", Vol. II, C. H. Li, Ed., Academic Press, New York, N.Y., 1973, pp 45–267.
(6) Abbreviations used are those recommended by IUPAC–IUB Commission on Biological Nomenclature: *J. Biol. Chem.*, **247**, 977 (1972). Others are: dcc, dicyclohexylcarbodiimide; DMF, dimethylformamide; DVB, divinylbenzene; HOBT, 1-hydroxybenzotriazole; HOSu, *N*-hydroxysuccinimide; Et_3N, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran.
(7) M. Bodanszky and J. T. Sheehan, *Chem. Ind. (London)*, 1597 (1966).
(8) S. S. Wang, *J. Org. Chem.*, **40**, 1235 (1975).
(9) Beckman Instruments, Inc., Spinco Division, Palo Alto, Calif. 94304.
(10) T. Curtius, *Ber.*, **35**, 3226 (1902).
(11) E. Schröder and K. Lübke, "The Peptides", Vol. I, Academic Press, New York, N.Y., 1965.
(12) Houben-Weyl, "Methoden der Organischen Chemie", Vol. 15, Part 1 and Part 2, "Synthese von Peptiden", E. Wünsch, Ed., Georg Thieme Verlag, Stuttgart, 1974.
(13) Although the comparisons were not made on an identical compound, the minor differences in their side chain protecting groups on Gly-Phe-Phe-Tyr-Thr sequence probably are not as important as to make the conclusions meaningless. The processes studied here dictated suitable combinations of protecting groups that could safely be used.
(14) B. Gutte and R. B. Merrifield, *J. Biol. Chem.* **246**, 1922 (1971).
(15) S. S. Wang, *J. Am. Chem. Soc.*, **95**, 1328 (1973).
(16) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).
(17) W. König, and R. Geiger, *Chem. Ber.*, **103**, 788 (1970).
(18) P. Sieber and B. Iselin, *Helv. Chim. Acta*, **51**, 614, 622 (1968).
(19) S. S. Wang and R. B. Merrifield, *Int. J. Protein Res.*, **1**, 235 (1969).
(20) The resin contained 0.55 mmol of Thr per gram according to N and amino acid analyses.
(21) F. Marchiori, R. Rochi, and E. Scoffone, *Gazz. Chim. Ital.*, **93**, 834 (1963).
(22) The dicyclohexylamine salt was converted into free acid prior to use.

Solid Phase Synthesis of Protected Peptides via Photolytic Cleavage of the α-Methylphenacyl Ester Anchoring Linkage

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Photolysis of α-methylphenacyl esters was adapted to solid phase peptide synthesis. Cleavage of the peptide to resin α-methylphenacyl ester anchoring bond by irradiation at 350 nm provided protected peptides in good yields. The process is examplified by the synthesis of Z-Lys(Z)-Phe-Phe-Gly-OH. For comparison, the same peptide was also prepared through photolytic cleavage of the *o*-nitrobenzyl ester anchoring linkage.

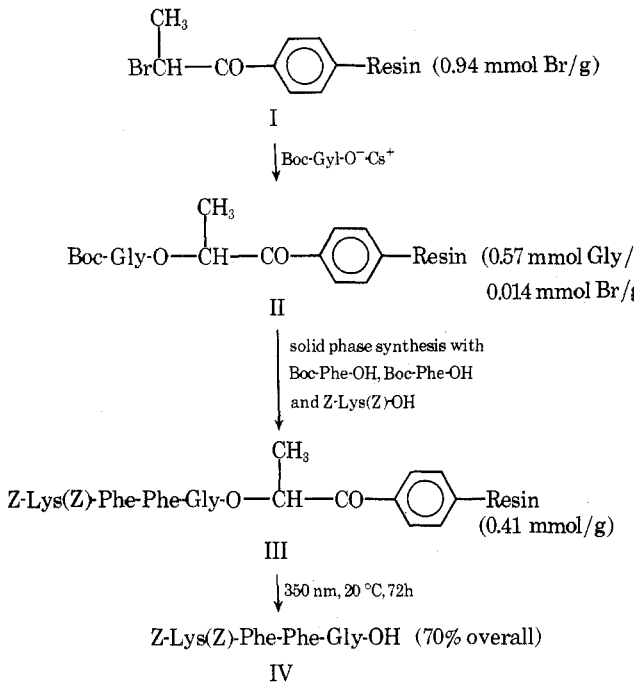
Studies on several photolyzable protecting groups that are potentially useful in peptide chemistry have recently been described in the literature.[1-11] Among these, the α-methylphenacyl ester[8] is of particular interest since it can readily be introduced into polymer matrices[12] and thus serve as an anchoring linkage between peptide chain and polymer support in solid phase synthesis.[13-17] Photolytic cleavage of this bond would therefore provide protected peptide intermediates that could subsequently be utilized in the synthesis of polypeptides by fragment condensation.[18-21]

In this report, the development of an efficient and convenient procedure for the preparation of protected peptides based on photolysis of the polymer linked α-methylphenacyl ester bond is described. A similar process involving photolytic cleavage of peptides from the *o*-nitrobenzyl ester resin[13] has recently been outlined.[10]

2-Bromopropionyl chloride was allowed to react with copolystyrene–2% divinylbenzene beads (200–400 mesh) in the presence of $AlCl_3$ as catalyst to form 2-bromopropionyl resin $BrCH(CH_3)CO$-C_6H_4-resin (I). The product contained 0.94 mmol of Br per gram of resin according to microanalysis. It showed an intense absorption band at 1685 cm^{-1} in the ir spectrum. The incorporation of Boc amino acids[22] into the resin was achieved by stirring I with a slight excess of Boc amino acid cesium salt[23] in dimethylformamide. The resultant Boc-HN-CHR-COO-CH-(CH_3)-CO-C_6H_4-resin (II) showed strong absorption bands at 1750 and 1725 cm^{-1} in addition to that at 1685 cm^{-1} in the ir spectrum. The degree of substitution is normally in the range of 0.5–0.7 mmol/g. There was practically no residual Br remaining after this treatment.

As outlined in Scheme I, Boc-Gly-OCH(CH_3)-CO-C_6H_4-resin (II) was deprotected, neutralized, and coupled with Boc-Phe-OH. The synthetic cycle was repeated with Boc-Phe-OH and then again with Z-Lys(Z)-OH. The

Scheme I. Preparation of Z-Lys(Z)-Phe-Phe-Gly-OH (IV) via Photolysis of the α-Methylphenacyl Ester Anchoring Bond



protected tetrapeptide resin Z-Lys(Z)-Phe-Phe-Gly-$OCH(CH_3)$-CO-C_6H_4-resin (III) thus obtained was then suspended in dimethylformamide and irradiated at 350 nm in a Rayonet photochemical reaction chamber for 72 h at 20 °C. The product Z-Lys(Z)-Phe-Phe-Gly-OH (IV) released from the resin was crystallized to give an analytically pure material in 70% overall yield. It was shown to be identical with a reference compound prepared by an alternate route.[24] The residual resin after photolysis retained 0.047 mmol/g of peptide according to amino acid analysis which indicated 92% photolytic cleavage under these conditions.

The stability of the α-methylphenacyl ester anchoring linkage of III under various conditions was studied. Rates of photolysis, hydrazinolysis, and acidolysis are shown in Figure 1. Photolysis proceeded rapidly with a half-life of approximately 5 h. The anchoring bond was completely stable against 50% trifluoroacetic acid in CH_2Cl_2 but surprisingly labile toward hydrazinolysis. For comparison, similar experiments were conducted with Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-CH_2-C_6H_4-resin (VII) and also with Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_4-resin (VIII), Figure 1. As expected, the polymer-bound benzyl ester linkage was completely stable to photolysis (350 mm) but rapidly cleaved by hydrazinolysis (10% H_2NNH_2 in dimethylformamide). In agreement with observations made by several investigators,[14,25] the benzyl ester anchoring linkage was cleaved slowly by 50% trifluoroacetic acid in CH_2Cl_2. The polymer bound o-nitrobenzyl ester in VII was photolyzed sluggishly under the conditions used. However, this bond is extremely sensitive to hydrazinolysis and completely inert toward 50% trifluoroacetic acid.

For preparation of Z-Lys(Z)-Phe-Phe-Gly-OH (IV) using $BrCH_2$-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-$CH_2C_6H_4$-resin (V), Merrifield resin (0.7 mmol Cl/g, 1% cross-linked, 200–400 mesh) was allowed to react with n-propylamine (see Scheme II). The amine resin was then acylated with 3-nitro-4-bromomethylbenzoic acid[10] to form V. Reaction of this material with the cesium salt[23] of Boc-Gly-OH afforded Boc-Gly-OCH_2-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-CH_2-C_6H_4-resin (VI). Solid phase synthesis was then continued by sequential incorporation of Boc-Phe-OH, Boc-Phe-OH, and Z-Lys(Z)-OH into the resin. The ensuing protected tetrapeptide resin VII was photolyzed at 350 nm to produce the desired compound IV in 40% overall yield. The lower yield of this process is due primarily to the slower rate of photolysis of this anchoring bond.

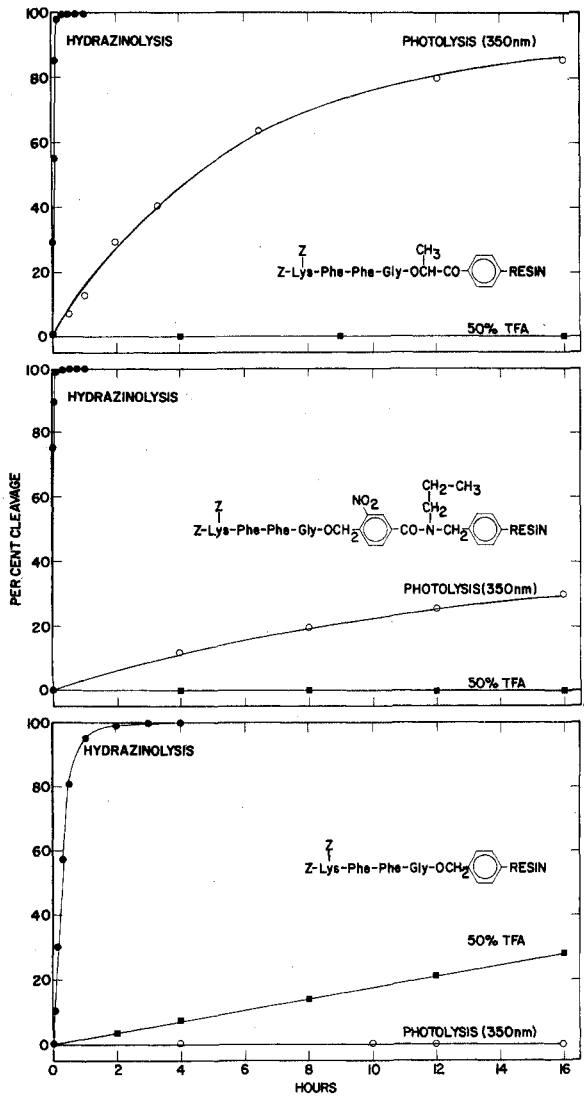


Figure 1. Cleavage of peptide resin α-methylphenacyl, o-nitrobenzyl, and benzyl ester anchoring bonds by photolysis, acidolysis, and hydrazinolysis (10% H_2NNH_2 in DMF). The rate of decrease in the peptide content (by amino acid analyses) of a resin was taken as the rate of cleavage of an anchoring bond.

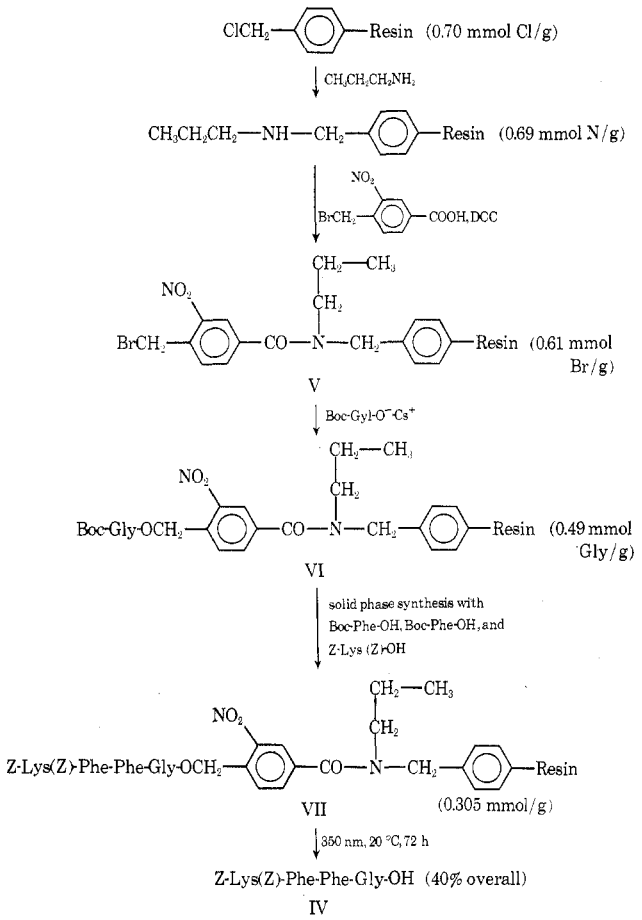
Preliminary experiments indicated that photolysis of the α-methylphenacyl ester anchoring linkage involving peptides with carboxyl terminal amino acids other than glycine (Ala, Leu, Thr(Bzl), Ile) was two to five times slower under similar conditions. Thus the process utilizing resin I as solid support would appear best suited for the synthesis of protected peptide fragments posessing carboxyl-terminal glycine residues.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer using KBr pellets. Thin layer chromatography was carried out on precoated silica gel plates (Merck F254) using solvent systems described previously.[26] Microanalyses, amino acid analyses, and other physicochemical measurements were performed by the Physical Chemistry Department.

Copolystyrene–2% divinylbenzene beads (200–400 mesh, Bio-Beads S-X2) was purchased from Bio-Rad Laboratories, Richmond, Calif. Amino acid derivatives were obtained from Bachem, Inc., Marina Del

Scheme II. Preparation of Z-Lys(Z)-Phe-Phe-Gly-OH (IV) via Photolysis of the o-Nitrobenzyl Ester Anchoring Bond



Ray, Calif., or prepared in this laboratory and were of L configuration. 2-Bromopropionyl chloride was bought from Aldrich Chemical Company, Milwaukee, Wis., and Cs_2CO_3 was from Gallard-Schlesinger Corp., N.Y. Other chemicals and solvents were reagent grade products from various commercial sources.

BrCH(CH$_3$)-CO-C$_6$H$_4$-Resin (I). 2-Bromopropionyl chloride (50 g, 243 mmol) was added slowly to a suspension of $AlCl_3$ (39 g) in 250 ml of CH_2Cl_2 with gentle stirring. The solid dissolved after a brief period of time, forming a light brown solution. It was cautiously added to a suspension of Bio-Beads S-X2 (216 g, 200–400 mesh) in 2200 ml of CH_2Cl_2 during a period of approximately 30 min. The mixture was stirred for an additional 17 h. The acylated resin thus obtained was collected and washed successively with CH_2Cl_2, nitrobenzene, and THF. The slightly brownish resin was stirred in a mixture of THF–H_2O (6000 ml, 2:1) for 30 min and collected by filtration. The operation was repeated twice more and the resin again washed with H_2O, THF, and then MeOH to give 248,3 g of light buff colored material: ir (KBr) 1685 cm^{-1}; Br, 7.50 (0.94 mmol/g); Cl, 0.06.

Boc-Gly-OCH(CH$_3$)-CO-C$_6$H$_4$-Resin (II). Boc-Gly-OH (4.38 g, 25 mmol) was dissolved in a mixture of 40 ml of EtOH and 10 ml of H_2O. The solution was titrated to pH 7.0 with 20% Cs_2CO_3. The mixture was evaporated to dryness (35 °C) and the residual solid was evaporated twice with fresh DMF. Boc-Gly-O^-·Cs^+ thus obtained was stirred with 20 g of I (18.8 mmol) in 80 ml of DMF for 17 h. The esterified resin was then collected and washed successively with DMF, DMF–H_2O, H_2O, THF–H_2O, THF, and MeOH to give 20.5 g of the desired product II. Amino acid analysis indicated the presence of 0.57 mmol Gly/g; Br, 0.11% (0.014 mmol/g); ir (KBr) 1750, 1725, 1685 cm^{-1}.

Similarly prepared were the resin analogues of Boc-Ala-OH (0.60 mmol Ala/g; 0.08% Br); Boc-Leu-OH (0.58 mmol Leu/g; 0.13% Br) and Boc-Thr(Bzl)-OH (0.62 mmol Thr/g; 0.07% Br).

Z-Lys(Z)-Phe-Phe-Gly-OH (IV). A. Ten grams of II (5.7 mmol) was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min), and coupled with Boc-Phe-OH (4.77 g, 18 mmol) for 120 min in CH_2Cl_2 using DCC (3.7 g, 18 mmol) as coupling reagent. Solid phase synthesis was continued by sequential incorporation of Boc-Phe-OH (4.77 g) and Z-Lys(Z)-OH (7.5 g, 18 mmol) to produce tetrapeptide resin III (12.7 g). Amino acid analysis indicated that this product contained 0.41 mmol of peptide per gram of resin. Amino acid composition Gly, 1.11; Phe, 1.94; Lys, 0.95. Nitrogen analysis, 3.04% (0.44 mmol peptide/g).

The protected tetrapeptide resin III (10 g, 4.1 mmol) was suspended in 250 ml of DMF that had been treated with argon gas (2 ml/s) for 15 min inside a jacketed Pyrex tube (3.5 × 30 cm). The suspension was further flushed with argon for an additional 60 min with gentle magnetic stirring. The reaction mixture was then tightly stoppered and irradiated at 350 nm (16 × 24 W) in a Rayonet photochemical reaction chamber for 72 h with efficient water cooling (20 °C). The released peptide was separated by suction filtration and the solvent removed at 40 °C under reduced pressure to give 3.5 g of clear oil which solidified immediately on treatment with ethyl acetate. It was crystallized from THF and water: yield 2.42 g (77%); mp 218–220 °C; $[\alpha]^{25}D$ −25.12° (*c* 1, DMF) [lit.[24] mp 220–222 °C; $[\alpha]^{25}D$ −25.55° (*c* 1, DMF)]; NMR and ir spectra identical with those of the reference compound.[24] No depression in mixture melting point.

Anal. Calcd for $C_{42}H_{47}N_5O_9$ (765.9): C, 65.87; H, 6.19; N, 9.14. Found: C, 65.82; H, 6.16; N, 9.24.

Amino Acid Anal. Gly, 0.96; Phe, 2.00; Lys, 1.03. Average recovery, 98%.

The residual resin (7.3 g) after photolytic cleavage contained 0.047 mmol of peptide according to amino acid analysis. It had amino acid composition of Gly, 0.88; Phe, 2.00; Lys 1.07. Thus, the photolysis can be calculated as 92% complete.

B. Resin VI (6.0 g, 2.94 mmol) was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min), and coupled with Boc-Phe-OH (1.93 g, 7.3 mmol) in the presence of DCC (1.54 g, 7.5 mmol) for 120 min. Solid phase synthesis was then continued with Boc-Phe-OH (1.93 g), followed by Z-Lys(Z)-OH (3.11, 7.5 mmol) in the next two cycles to give protected tetrapeptide resin VII (7.9 g). Amino acid analysis indicated that there was 0.305 mmol of peptide per gram of resin. Resin VII (7.0 g, 2.14 mmol) was photolyzed as described in A at 350 nm for 72 h. The released peptide was worked up as above: yield 0.80 g (48.7%); mp 211–215 °C; $[\alpha]^{25}D$ −25.32° (*c* 1, DMF); NMR and ir spectra identical with those of the reference.[24]

Anal. Found: C, 65.94; H, 6.28; N, 9.04.

BrCH$_2$-C$_6$H$_3$(3-NO$_2$)-CO-N(CH$_2$CH$_2$CH$_3$)-CH$_2$C$_6$H$_4$-Resin (V). Chloromethyl resin (10 g, 7 mmol) was suspended in DMF (100 ml) and stirred with 11 ml of *n*-propylamine for 70 h. The resin was washed with DMF, THF, and MeOH to provide 10.1 g of $CH_3CH_2CH_2$-NH-CH_2-C_6H_4-resin (N, 0.97; Cl, 0.09). It was washed several times with CH_2Cl_2 and suspended in 150 ml of CH_2Cl_2 when 2.35 g of 3-nitro-4-bromomethylbenzoic acid[10] (9 mmol) and 2.0 g of DCC (9.7 mmol) were added. After stirring for 2 h the resin was collected and washed as usual yielding 11.5 g of desired product V (N, 0.86; Br, 4.88). The resin absorbed strongly at 1600 cm^{-1} in the ir spectrum.

Boc-Gly-OCH$_2$-C$_6$H$_3$(3-NO$_2$)-CO-N(CH$_2$CH$_3$CH$_3$)-CH$_2$-C$_6$H$_4$-Resin (VI). Boc-Gly-OH (0.7 g, 4 mmol) was dissolved in 8 ml of *i*-PrOH plus 2 ml of H_2O and the mixture titrated to pH 7.0 with 20% Cs_2CO_3. The solution was evaporated to dryness, reevaporated twice with DMF (40 °C), and then stirred in DMF (25 ml) with 6 g of V (3.68 mmol) for 24 h. The resin was then washed as usual and dried to give 6.2 g of material. Amino acid analysis indicated that there was 0.49 mmol of glycine per gram of resin. There was virtually no residual bromide left (0.13%). There were strong absorption bands at 1750, 1710, and 1600 cm^{-1}.

Z-Lys(Z)-Phe-Phe-Gly-OCH$_2$-C$_6$H$_4$-Resin (VIII). Hydroxymethyl resin (4 g, 2.8 mmol), prepared as described before,[26] was allowed to react with Boc-Gly-OH (0.98 g, 5.6 mmol), 4-dimethylaminopyridine (0.69 g, 5.6 mmol), and DCC (1.2 g, 5.9 mmol) in CH_2Cl_2 (55 ml) for 120 min. The resin was collected and washed to give 4.32 g of material. Amino acid analysis indicated that the product, Boc-Gly-OCH_2-C_6H_4-resin, contained 0.58 mmol Gly/g. After benzoylation,[26] the resin was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min), and coupled (120 min) with Boc-Phe-OH (1.32 g, 5 mmol) in the presence of DCC (1.03 g, 5 mmol). Continuation of solid phase synthesis with Boc-Phe-OH (1.32 g) in the next cycle followed by Z-Lys(Z)-OH (2.07 g, 5 mmol) in another cycle gave Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_4-resin (4.9 g). Amino acid analysis showed that the resin contained 0.51 mmol peptide/g with an amino acid composition of Gly, 1.02; Phe, 1.98; Lys, 1.00.

Rates of Cleavage of Peptide α-Methylphenacyl, o-Nitrobenzyl, and Benzyl Ester Anchoring Bonds by Photolysis, Acidolysis, and Hydrazinolysis. The protected tetrapeptide resin III (2.0 g) was suspended in 50 ml of argon-saturated DMF and irradiated at 350 nm in the manner described for the preparation of IV. At dif-

ferent time intervals aliquots (4 ml) were withdrawn (under argon) and the resin separated immediately by suction filtration, washed thoroughly with DMF, CH_2Cl_2, and MeOH, and then subjected to amino acid analysis. The rate of decrease in amino acid content was taken as the rate of photolysis of the α-methylphenacyl ester anchoring bond. Exactly the same experiments were performed on tetrapeptide resins VII and VIII to determine the rate of photolytic cleavage of the o-nitrobenzyl and benzyl ester linkages. The results are summarized in Figure 1. For the studies of the rates of acidolysis or hydrazinolysis of the resins III, VII, and VIII, 0.5 g each of the samples were stirred individually in 20 volumes each of TFA–CH_2Cl_2 (1:1) or 10% H_2NNH_2 (DMF) in six separate flasks. Aliquots (1 ml) from each reaction were taken at different times and treated as described above for the photolysis experiments. The results are also shown in Figure 1.

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Registry No.—IV, 40099-54-5; copolystyrene divinylbenzene, 9003-70-7; 2-bromopropionyl chloride, 7148-74-5; Boc-Gly-OH, 4530-20-5; Boc-Phe-OH, 13734-34-4; Z-Lys(Z)-OH, 405-39-0.

References and Notes

(1) J. A. Barltrop, P. J. Plant, and P. Schofield, *Chem. Commun.*, 822 (1966).
(2) J. W. Chamberlin, *J. Org. Chem.*, **31**, 1658 (1966).
(3) A. Patchornik, B. Amit, and R. B. Woodward, *J. Am. Chem. Soc.*, **92**, 6333 (1970).
(4) J. C. Sheehan, R. M. Wilson, and A. W. Oxford, *J. Am. Chem. Soc.*, **93**, 7222 (1971).
(5) C. Birr, W. Lochinger, G. Stahnke, and P. Lang, *Justus Liebigs Ann. Chem.*, **763**, 162 (1972).
(6) U. Zehavi and A. Patchornik, *J. Am. Chem. Soc.*, **95**, 5673 (1973).
(7) B. Amit and A. Patchornik, *Tetrahedron Lett.*, 2205 (1973).
(8) J. C. Sheehan and K. Umezawa, *J. Org. Chem.*, **38**, 3771 (1973).
(9) B. Amit, U. Zehavi and A. Patchornik, *J. Org. Chem.*, **39**, 192 (1974); *Isr. J. Chem.*, **12**, 103 (1974).
(10) D. H. Rich and S. K. Gurwara, *J. Am. Chem. Soc.*, **97**, 1575 (1975).
(11) D. H. Rich and S. K. Gurwara, *Tetrahedron Lett.*, 301 (1975).
(12) T. Mizoguchi, K. Shigezane, and N. Takamura, *Chem. Pharm. Bull.*, **18**, 1465 (1970).
(13) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(14) R. B. Merrifield in "The Chemistry of Polypeptides", P. G. Katsoyannis, Ed., Plenum Press, New York, N.Y., 1973, pp 335–361.
(15) G. R. Marshall and R. B. Merrifield in "Biochemical Aspects of Reactions on Solid Supports", G. R. Stark, Ed., Academic Press, New York, N.Y., 1971, pp 111–169.
(16) J. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969.
(17) J. Meienhofer in "Hormonal Proteins and Peptides", Vol. 2, C. H. Li, Ed., Academic Press, New York, N.Y., 1973, pp 45–267.
(18) S. S. Wang and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **4**, 309 (1972).
(19) E. Schröder and K. Lübke, "The Peptides", Vol. 1, Academic Press, New York, N.Y., 1965.
(20) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis", Interscience, New York, N.Y., 1966.
(21) Houben-Weyl, "Methoden der Organischen Chemie", Vol. 15, Part 1 and Part 2, "Synthese von Peptiden", E. Wünsch, Ed., Georg Thieme Verlag, Stuttgart, 1974.
(22) Abbreviations used: Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; DCC, dicyclohexylcarbodiimide; DMF, dimethylformamide; THF, tetrahydrofuran; TFA, trifluoroacetic acid; Z, benzyloxycarbonyl.
(23) B. F. Gisin, *Helv. Chim. Acta*, **56**, 1476 (1973).
(24) S. S. Wang, *J. Am. Chem. Soc.*, **95**, 1328 (1973).
(25) B. Gutte and R. B. Merrifield, *J. Biol. Chem.*, **246**, 1922 (1971).
(26) S. S. Wang, *J. Org. Chem.*, **40**, 1235 (1975).

Total Synthesis of Sativene and Copacamphene via a Free Radical Cyclization

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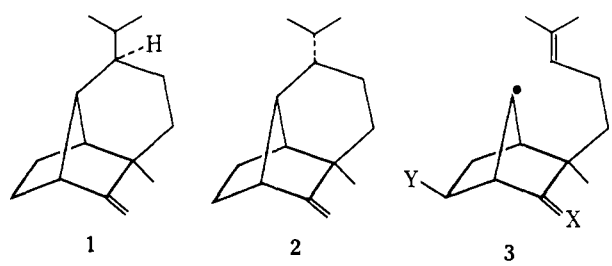
A synthesis of the tricyclic sesquiterpenes sativene (1) and copacamphene (2) is described, the key carbon–carbon bond formation being effected via a free-radical cyclization of the bicyclic compound 3 (X = O; Y = H). A new method for transforming a terminal olefin to an aldehyde via the corresponding alkyl phenyl sulfide followed by oxidation with *N*-chlorosuccinimide and hydrolysis of the resulting chloroalkyl phenyl sulfide is used to prepare the aldehyde precursor of 3.

The tricyclic sesquiterpenes sativene (1) and copacamphene (2) possess five chiral centers and thus offer interesting substrates to test and develop synthetic methodology.[1] While schemes based on heterolytic processes leading to carbon–carbon bond formation have been responsible for all but a handful of synthesis, one can expect[2] that homolytical processes, at least in isolated steps, will become more and more common as traditional prejudices against free-radical intermediates are removed.[3] Accordingly, we sought to develop a synthetic scheme based on free-radical intermediates which might be used to synthetize not only sativene and copacamphene, but also structurally related compounds such as cyclosativene, isosativene, and longifolene.

The key intermediate of our projected synthesis was the free radical 3, which could be expected[4] to cyclize to the tricyclic skeleton found in 1 and 2. Unfortunately, the factors controlling stereoselectivity of free-radical cyclizations are not understood, but because of the strained nature of the 7-norbornyl radical[5] and the expected stability of the tertiary radical produced, the product ratio should reflect kinetic and not thermodynamic factors. However, no clear prediction of the stereoselectivity expected could be made by consulting Dreiding models of radical 3. This steric ambiguity was offset by the choice of the norbornanone skeleton as the starting point of the synthesis, the other four asymmetric centers being controlled by the topological and steric restraints of the bicyclic ring structure.



1 2 3

Of the variety of methods that could be used to synthesize the desired radical 3, the Barton reaction appeared to have several advantages since the desired precursors should be